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ORIGINAL REPORT

# Healthcare databases in Europe for studying medicine use and safety during pregnancy

Rachel A. Charlton<sup>1\*</sup>, Amanda J. Neville<sup>2</sup>, Sue Jordan<sup>3</sup>, Anna Pierini<sup>4</sup>, Christine Damase-Michel<sup>5</sup>, Kari Klungsøyr<sup>6,7</sup>, Anne-Marie Nybo Andersen<sup>8</sup>, Anne Vinkel Hansen<sup>9</sup>, Rosa Gini<sup>10</sup>, Jens H. J. Bos<sup>11</sup>, Aurora Puccini<sup>12</sup>, Caroline Hurault-Delarue<sup>5</sup>, Caroline J. Brooks<sup>13</sup>, Lolkje T. W. de Jong-van den Berg<sup>11</sup> and Corinne S. de Vries<sup>1</sup>

<sup>1</sup>Department of Pharmacy and Pharmacology, University of Bath, Bath, UK

<sup>2</sup>IMER (Emilia-Romagna Registry of Birth Defects), Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy

<sup>3</sup>Department of Nursing, College of Human and Health Sciences, Swansea University, Swansea, Wales, UK

<sup>4</sup>Institute of Clinical Physiology, National Research Council (IFC-CNR), Pisa, Italy

<sup>5</sup>Pharmacologie, Médicale, Faculté de Médecine, Université de Toulouse III, INSERM UMR1027, Toulouse, France

<sup>6</sup>Medical Birth Registry of Norway, The Norwegian Institute of Public Health, Oslo, Norway

<sup>7</sup>Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

<sup>8</sup>Section of Social Medicine, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

<sup>9</sup>Hospital Lillebaelt, Kolding, Denmark

<sup>10</sup>Agenzia Regionale di Sanità della Toscana, Florence, Italy

<sup>11</sup>Pharmacoepidemiology and Pharmacoeconomics Unit, Department of Pharmacy, University of Groningen, Groningen, The Netherlands

<sup>12</sup>Drug Policy Service, Emilia-Romagna Region Health Authority, Bologna, Italy

<sup>13</sup>Institute of Life Science, College of Medicine, Swansea University, Swansea, Wales, UK

## ABSTRACT

**Purpose** The aim of this study was to describe a number of electronic healthcare databases in Europe in terms of the population covered, the source of the data captured and the availability of data on key variables required for evaluating medicine use and medicine safety during pregnancy.

**Methods** A sample of electronic healthcare databases that captured pregnancies and prescription data was selected on the basis of contacts within the EUROCAT network. For each participating database, a database inventory was completed.

**Results** Eight databases were included, and the total population covered was 25 million. All databases recorded live births, seven captured stillbirths and five had full data available on spontaneous pregnancy losses and induced terminations. In six databases, data were usually available to determine the date of the woman's last menstrual period, whereas in the remainder, algorithms were needed to establish a best estimate for at least some pregnancies. In seven databases, it was possible to use data recorded in the databases to identify pregnancies where the offspring had a congenital anomaly. Information on confounding variables was more commonly available in databases capturing data recorded by primary-care practitioners. All databases captured maternal co-prescribing and a measure of socioeconomic status.

**Conclusion** This study suggests that within Europe, electronic healthcare databases may be valuable sources of data for evaluating medicine use and safety during pregnancy. The suitability of a particular database, however, will depend on the research question, the type of medicine to be evaluated, the prevalence of its use and any adverse outcomes of interest. © 2014 The Authors. *Pharmacoepidemiology and Drug Safety* published by John Wiley & Sons, Ltd.

**KEY WORDS**—electronic medical records; automated data; pregnancy; teratogens; pharmacoepidemiology

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## INTRODUCTION

Medication use during pregnancy is common,<sup>1–5</sup> and for some classes of medicine, such as selective serotonin

reuptake inhibitors, there has been an increase in prescribing over time.<sup>6</sup> The safety of a medicine when used during pregnancy is often unknown at the time of market approval. This is largely due to the limited ability of animal studies to predict human teratogenesis and the fact that pregnant women are typically excluded from pre-marketing randomised controlled clinical

\*Correspondence to: R. Charlton, Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath, BA2 7AY, UK.  
Email: r.a.charlton@bath.ac.uk

trials.<sup>7</sup> The safety of medicine use during pregnancy can therefore only be evaluated post-marketing.

Over the last 50 years, a number of surveillance methods have been introduced including spontaneous reporting, case-control surveillance systems and pregnancy exposure registries. These methods have some limitations, however, particularly in relation to voluntary reporting and small sample sizes. It is these limitations that have contributed to the expansion of the use of electronic healthcare databases, containing anonymised patient data, for evaluating the safety of medicine use during pregnancy.

When evaluating the safety of medicine use during pregnancy, the reliability of exposure and outcome assessment are important considerations. Electronic healthcare databases can often provide detailed data on potential prescription drug exposure, although they lack information on non-compliance, over-the-counter medicine use (medicines purchased without a prescription) and the precise timing of exposure.

In terms of outcome data, although information on pregnancy losses may be captured, the level of detail regarding congenital anomalies in the offspring can be limited, and this can hamper drug safety in pregnancy research using healthcare databases alone.<sup>8</sup> In Europe, the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) comprises 43 registries of congenital anomaly registrations in 23 different countries.<sup>9</sup> These registries capture detailed and extensive outcome information regarding the specific types of congenital anomaly although there may be underreporting in some registries, and information on medicine exposure *in utero* can be limited. A study evaluating first-trimester exposure to the anticonvulsant lamotrigine and the risk of oral clefts in the offspring was the first study to use EUROCAT congenital anomaly data, including the medication exposure data routinely recorded by the registries, to carry out a risk assessment.<sup>10</sup> This work is now being developed further within EUROMediCAT, a Seventh Framework Programme study funded by the European Commission that aims to make more systematic use of electronic healthcare databases in combination with EUROCAT congenital anomaly data and build a European system for the evaluation of medicine use in pregnancy in relation to the risk of congenital anomalies. This paper describes eight electronic healthcare databases in Europe contributing to EUROMediCAT.

## METHODS

A sample of electronic healthcare databases that captured pregnancies and prescription data was selected for

this study on the basis of contacts within the EUROCAT network. For each participating database, an inventory was completed to provide information on the population covered, the source of the data captured and the availability of data on key variables required for evaluating medicine use during pregnancy as well as pregnancy outcomes. This inventory was completed on the basis of the data available within these databases between 2004 and 2012. Ethical and data access approvals were obtained from the relevant governance infrastructures.

## RESULTS

Seven databases were selected to participate in the study: two in the UK,<sup>11–13</sup> two in Italy<sup>4,14,15</sup> and one each in Denmark,<sup>16–18</sup> the Netherlands<sup>3,19</sup> and Norway.<sup>20–22</sup> Mid-way through the study, an eighth centre from France also offered to collaborate.<sup>23</sup> With the exception of the IADB.nl database in the Netherlands and the Clinical Practice Research Datalink (CPRD) in the UK, all databases involved the linkage of multiple individual databases to enable the capture of pregnancies, prescription data and additional information on potential confounding variables. For the remainder of this paper, linked databases will be referred to as a single database. A summary of the eight databases can be found in Table 1.

### *Population covered*

The total population covered by the eight databases was 25 million. The Danish and Norwegian databases covered the entire population in each country whereas those in the Netherlands, France and Italy covered a particular region (Northern Netherlands, Haute Garonne, Emilia-Romagna and Tuscany), and the databases in the UK captured a sample of the population (the CPRD capturing ~8% of the UK population and the Secure Anonymised Information Linkage (SAIL) database capturing approximately 40% of the population of Wales). The potential for loss to follow-up varied between databases with patients in Denmark, Norway and Italy only leaving as a result of death or emigrating from the country/region, whereas in other databases, exit from the database could result, for example, from the patient changing general practitioner (GP) or the GP practice withdrawing from the database.

### *Exposure data*

The databases in the UK captured exposure data based on the issue of a prescription whereas all other databases captured pharmacy dispensing data and therefore only

Table 1. Overview of the databases

	Country/region							
	Netherlands	Denmark	Norway	Italy—Emilia-Romagna	Italy—Tuscany	UK	Wales	France
Involves database record linkage	No	Yes	Yes	Yes	Yes	No	Yes*	Yes <sup>†</sup>
Population base	500 000	5 000 000	4 800 000	4 200 000	3 700 000	5 000 000 <sup>‡</sup>	2 000 000 <sup>§</sup>	1 200 000
Database for live and stillbirth pregnancy identification	IADB.nl database	Danish National Birth Registry	of Norway Medical Birth Registry	Certificate of Delivery Assistance (CeDAP)	Certificate of Delivery Assistance (CeDAP) Hospital Discharges Registry	Clinical Practice Research Datalink (CPRD)**	National Community Health Database (NCCHD)	Mother and Child Protection Centre (PMI) and Hospital Medical Information System databases (PMSI)
Database for pregnancy loss identification	N/A	Danish National Patient Registry	of Norway Medical Birth Registry	N/A	Discharges for Induced Terminations and Spontaneous Abortions. Hospital Discharges Registry	Clinical Practice Research Datalink	Patient Episode Database for Wales (PEDW)	Antenatal Diagnostic Centre database (CDA) and PMSI
Database for medicine use data	IADB.nl database	Danish Prescription Registry	Norwegian Prescription Database	Emilia-Romagna Prescription Database (ERP)	Tuscany Prescription Database (TPD)	Clinical Practice Research Datalink	The General Practice (GP) Dataset	French Health Insurance System Database (CPAM)
Source for medicine use data	Pharmacy dispensing	Pharmacy dispensing	Pharmacy dispensing	Pharmacy dispensing <sup>††</sup>	Pharmacy dispensing and Healthcare Facilities Dispensing (except hospitals) <sup>††</sup>	GP practice prescribing <sup>‡‡</sup>	GP practice prescribing <sup>‡‡</sup>	Pharmacy dispensing
Start of first data collection <sup>§§</sup>	1995	1996***	2004 <sup>†††</sup>	2003	2003	1987	1987	2004
Capture outpatient prescribing	Yes	Yes	Yes	Yes <sup>††</sup>	Yes <sup>††</sup>	Yes	Yes	Yes
Capture inpatient prescribing	No	No	No	No	No	Some	Some	No
Medical coding system	N/A	ICD-10	ICD-10	ICD-9/10	ICD-9	Read	Read	N/A
Opportunity to request additional data	No	Yes <sup>‡‡‡</sup> , ****	Yes	No	No	Yes <sup>‡‡‡</sup>	Yes****	Yes <sup>††††</sup>

N/A, not available; ICD, International Classification of Diseases.

\*Secure Anonymised Information Linkage (SAIL) databank.

†EFEMERIS database.

‡The size of the population captured by the CPRD has grown steadily over time and was approximately 5.0 million in May 2012.

§The Child Health Database and Patient Episode Database capture the whole population of Wales (three million), whereas the General Practice Dataset currently contains around two million records.

\*\*Previously the General Practice Research Database (GPRD).

††Including only products reimbursed by the Italian National Health Service and excluding those dispensed to outpatients in a hospital pharmacy.

‡‡Including non-GP prescribers working within the GP practice.

§§For many databases, the data have become richer over time, and additional data sources have become available.

\*\*\*The Danish National Prescription Registry has been collecting prescriptions since 1995, and the Birth and Patient registries of Norway go further back.

††††The Norwegian Prescription Database started collecting prescription data in 2004, but the Norwegian Medical Birth Registry has been collecting pregnancy outcome data since 1967.

\*\*\*\*Opportunity to review against charts and to request further information via questionnaires.

†††††Opportunity to request linkage to other datasets.

††††††Opportunity to request further information only for medical abortions.

those prescriptions actually dispensed (Table 1). The majority of databases did not capture prescriptions issued to inpatients during a hospital stay; in the UK databases, however, some were captured if the GP entered them following receipt of a hospital letter. In Denmark, Norway and the Netherlands, all other prescriptions were captured, including private prescriptions, although a small number of rare or expensive medicines (e.g. cancer treatments) may not have been captured if they were dispensed at the hospital to outpatients. In the French database, all prescriptions for reimbursed drugs were captured, regardless of whether they had been prescribed by a GP or a specialist or had been issued privately. In the Italian databases, prescriptions reimbursed by the National Health Service were captured; however, the majority of private prescriptions and prescriptions issued by a specialist to outpatients that were dispensed at a hospital pharmacy were not captured; the extent of hospital dispensing to outpatients varied by product and drug class. In the UK databases, the majority of prescriptions captured were those issued by a GP or non-GP prescriber within primary care. Private prescriptions and prescriptions initiated by a specialist in a hospital outpatient department were largely not captured, but any repeat prescriptions that were subsequently issued by the GP were captured.

Determining the precise timing of exposure is crucial when evaluating medicine use and safety during pregnancy. To do this, accurate information on the first day of the last menstrual period (LMP) is required. Some databases such as those in Denmark, France and Norway have this information or can calculate it on the basis of gestational age at delivery for the majority of pregnancies. In other databases, such as the CPRD, information on the LMP is only sometimes recorded, and algorithms need to be created to determine a best estimate (Table 2).

### Pregnancies captured

Table 2 summarises pregnancy-related information for each of the databases. The number of pregnancies captured per year varied from ~2000 in the Netherlands to ~88 000 in Denmark. This variation reflects the difference in the size of the source populations covered and the types of pregnancy outcomes captured. All databases captured live and stillborn deliveries with the exception of the IADB.nl database where stillbirth data were not available. Induced terminations of pregnancy and spontaneous pregnancy losses were captured in all databases, except those in the Netherlands and Emilia-Romagna (Tables 1 and 2). In the Norwegian Medical Birth Registry, however, induced terminations after 12 weeks' gestation were only registered when

the foetus had a congenital anomaly and spontaneous abortions were underreported, particularly those occurring before 16 weeks' gestation. Although the databases in Wales and Tuscany captured data on pregnancy losses, in Wales, the data are considered too sensitive to release for research, and in Tuscany, most could not be linked to prescription data. None of the databases captured very early pregnancy losses that occur before the pregnancy is clinically recognised.

### Outcome data

The most frequently studied adverse pregnancy outcome following *in utero* medication exposure is the risk of major congenital anomalies. It was possible to identify congenital anomalies in pregnancies that ended in a live or stillbirth in all databases, with the exception of the IADB.nl database.<sup>1</sup> In Denmark and Norway, congenital anomaly data could be obtained from the national birth registers, and in Italy, they were captured through the 'Certificate of Delivery Assistance'. In the CPRD, congenital anomalies could be identified from the infants' GP records; in Wales, they could be identified from linking to the congenital anomalies database; and in France, they could be identified from the Mother and Child Protection Centre database and the Antenatal Diagnostic Centre database for induced abortions. Identification of pregnancies that were terminated following a pre-natal diagnosis of a congenital anomaly was largely restricted to databases that captured induced terminations of pregnancy. The completeness and reliability of recording of congenital anomalies, along with the level of detail, may vary between databases and by specific type of anomaly. Within some databases, there is the opportunity to request additional non-coded data, full paper medical records or to send questionnaires that can help verify or refute diagnoses recorded in the coded data (Table 1). In addition to information on congenital anomalies, some databases were able to provide data on other adverse pregnancy outcomes such as prematurity, low or high birth weight and intrauterine growth retardation (Table 2).

### Data on potential confounding variables

Table 3 summarises the availability of data on potential confounding variables. Information on smoking status and alcohol intake was more commonly available in databases that captured data recorded in primary care,

<sup>1</sup>Congenital anomalies are not recorded in the database itself; however, congenital anomalies can be identified via the North Netherlands EUROCAT registry.



Table 2. Pregnancy information captured by the different databases

	Country/region					
	Netherlands	Denmark	Norway	Italy—Emilia-Romagna	Italy—Tuscany	UK
Database(s) that capture pregnancy data	IADB.nl database	Danish National Birth Registry and Danish National Patient Registry	Medical Birth Registry of Norway	Emilia-Romagna CeDAP	Tuscany CeDAP and the Discharges for Induced Terminations and Spontaneous Abortions Database	Clinical Practice Research Datalink
Annual number of pregnancies*	~2000	~88 000	~60 000	~40 000	~32 000	~80 000
Total number of pregnancies in the database in 2012	27 000	1 300 000†	532 000	350 000	300 000	1 000 000
Captures stillbirths	No	Yes	Yes	Yes	Yes	Yes
Captures induced terminations of pregnancy	No	Yes	Yes§	No	Yes**	Yes
Captures spontaneous abortions	No	Yes	Some§§	No	Yes**	Yes
Percentage of pregnancies resulting in a loss	NA	30	0.9	NA	25	30
Can identify multiple births (e.g. twins)	Yes	Yes	Yes	Yes	Yes	Yes
Date of last menstrual period available	Estimated	Calculated from gestational age	Yes	Calculated from gestational age	Calculated from gestational age	Yes for ~40%, estimated for ~60%
Data on birth weight	No	Most births	Yes	Yes	Yes	Yes for ~80%, estimated for ~20%
Data on gestational age	No	Yes	Yes	Yes	Yes	Yes
including prematurity	No	Yes	Yes	Yes	Yes	Yes
Able to identify congenital anomalies	No***	Yes	Yes	Yes	Yes	Yes
Data on intrauterine growth retardation	No	Some	Yes	Yes	No	Some
Data on developmental delay in childhood	No	Some	No	No	No	Yes

NA, not available.

\*Including pregnancy losses where captured.

†In December 2010.

‡Only women hospitalised in the University Hospital of Toulouse (PMSI database).

§Those occurring from 12 weeks' gestation with a congenital anomaly.

\*\*Pregnancy losses are captured but access is restricted, and these data are not currently available for research.

††Pregnancy losses are captured by the database, but the majority cannot be linked to prescription data.

‡‡All medical abortions (CDA database) but only induced abortions performed in the University Hospital (CHU) of Toulouse (PMSI database).

§§Compulsory notification of those occurring from 12 weeks' gestation although some underreporting especially for those occurring at less than 16 weeks.

\*\*\*Only women followed in the University Hospital of Toulouse (PMSI database).

†††For spontaneous abortions, induced abortions and intrauterine death, data are only available if women consulted the University Hospital of Toulouse (PMSI database).

‡‡‡Congenital anomalies are not recorded in the database itself; however, congenital anomalies can be identified via the North Netherlands EUROCAT registry.

§§§At 9 and 24 months.

Table 3. Covariate data recorded in each of the databases

	Country/region							
	Netherlands	Denmark	Norway	Italy—Emilia-Romagna	Italy—Tuscany	UK	Wales	France
Databases	IADB.nl database	Danish National Birth Registry, Patient Registry and Prescription Registry	Medical Birth Registry of Norway and Prescription Database	Emilia-Romagna (CeDAP + ERPD)	Tuscany (CeDAP + TPD)	General Practice Research Database	Secure Anonymised Information Linkage (SAIL) Databank	EFEMERIS
Smoking status	No	Yes*	Yes <sup>†</sup>	Yes	Yes	Yes	Some	Some <sup>‡</sup>
Alcohol consumption	No	No	No	No	No	Yes	Some	Some <sup>‡</sup>
Pre-pregnancy body mass index	No	Yes*	No	No <sup>§</sup>	Yes	Yes	Some	No
A measure of socioeconomic status	Yes**	Yes <sup>††</sup>	Yes <sup>‡‡</sup>	Yes <sup>††</sup>	Yes <sup>††</sup>	Yes <sup>§§</sup>	Yes***	Yes <sup>†††</sup>
Maternal co-prescribing	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Standard-dose folic acid (0.4 mg)	No	No	Most	Some	Some	Some—when prescribed	Some—when prescribed <sup>‡‡‡</sup>	Most <sup>§§§</sup>
High-dose folic acid (5 mg)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Most <sup>§§§</sup>
Indication for prescribing	No	Some	Yes****	No	No	Majority	Some	No
Maternal co-morbidity	No	Yes	Yes	No	No	Yes	Yes	Some <sup>††††</sup>
Family history of congenital anomalies	No	Some	Yes	Yes	Yes	No	No	For medical terminations
Maternal occupation	No	No	No	Yes	No	No	No	Yes <sup>‡‡‡‡</sup>
Maternal age at pregnancy start	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

\*Available for pregnancies that result in a delivery but not for those that end in a pregnancy loss.

<sup>†</sup>Available for deliveries and spontaneous abortions but not induced terminations.

<sup>‡</sup>Only for births, but data often missing (children certificates (PMI database)).

<sup>§</sup>Not for the majority of the study period but available from 2012 in CeDAP.

\*\*Based on address/postcode.

<sup>††</sup>Based on maternal education level.

<sup>‡‡</sup>Available for all mothers registered in the MBRN and when the outcome is a termination of pregnancy owing to a congenital malformation through linkage with the Education Database of Norway.

<sup>§§</sup>Available at a patient and practice level based on the Index of Multiple Deprivation (IMD) score, based on address and postcode.

<sup>\*\*\*</sup>Based on Townsend scores and ranks and Welsh Index of Multiple Deprivation.

<sup>†††</sup>Based on maternal occupation—only available for live births.

<sup>‡‡‡</sup>All prescriptions are free in Wales so women may prefer to get a prescription rather than buy it over the counter without a prescription.

<sup>§§§</sup>Both high-dose and low-dose folic acid are available over the counter without a prescription, but both can be reimbursed, so women prefer to have them prescribed.

<sup>\*\*\*\*</sup>Only for reimbursed prescriptions.

<sup>††††</sup>For medical abortions and births (hypertension, diabetes, pre-eclampsia and open response).

<sup>‡‡‡‡</sup>Only for live births.

although smoking status was available for the majority of pregnancies ending in a live delivery in the Italian, Danish and Norwegian databases. Data on pre-pregnancy body mass index (BMI) were available for the majority of patients in the CPRD and Tuscany databases. In Denmark, smoking status and BMI data were not

recorded in the Patient Registry and were therefore only available for deliveries. Limited data on smoking and alcohol use were available in France. Data on socioeconomic status were captured in all databases.

All databases had the potential to capture data on additional medicines being prescribed or dispensed to

women other than the medicine specifically being evaluated as part of a study (maternal co-prescribing). None of the databases, however, captured data on medicines bought over the counter, which often includes standard-dose 0.4 mg folic acid. As a result, information on folic acid exposure, which reduces the risk of some congenital anomalies when taken during the periconceptional period,<sup>24,25</sup> was often restricted to women who received the higher 5-mg dose, which in most countries is only available on prescription (Table 3).

Availability of data on the indication for prescribing varied between databases. In the Norwegian prescription database, this information was available for all medicines that were reimbursed, although the level of detail on the indication has improved since 2009. In Denmark, some information on indication for prescribing could be inferred from hospital diagnoses prior to prescription. In the CPRD and SAIL, the patients' full medical records were available, and the indication for prescribing could be inferred from diagnoses recorded on or around the same date as a prescription for a particular product. No data on the indication for prescribing were available within the French, Italian or Dutch databases.

For the UK and Danish databases, diagnoses of maternal comorbidities could be obtained from the same data sources as those used for the indication of prescribing. In Norway, however, information on chronic diseases that the woman had before pregnancy was recorded in the Medical Birth Registry. In France, only data on hypertension during pregnancy, gestational diabetes and pre-eclampsia were available. No data on maternal comorbidities were available within the Italian or Dutch databases, although for some chronic conditions, it may be possible to use prescription records as proxies. Recording of a family history of congenital anomalies was rare, and none of the databases captured information on maternal diet.

## DISCUSSION

Eight electronic healthcare databases that capture useful information regarding medicine use during pregnancy and a range of pregnancy outcomes have been described. To our knowledge, this paper is the first to provide a comprehensive overview of the populations covered by these databases, the types of data captured and the information available regarding variables required for the study of medicine use and safety during pregnancy.

### *Sample size considerations*

One of the strengths of electronic healthcare databases is the large number of pregnancies they capture.

Congenital anomalies are rare and arise from different embryonic tissues and at different gestational stages. As a consequence, the mechanism and timing of interference with embryogenesis will differ, and individual anomalies need to be considered separately, rather than amalgamated under a single all-embracing congenital anomaly category.<sup>26</sup> In addition, the exposures of interest may be relatively uncommon in pregnancy, and most medicines need to be evaluated individually, as often a 'class effect' cannot be assumed.<sup>7</sup> A classic example is the difference in teratogenicity of glutethimide, which is not a major teratogen, and its derivative thalidomide. Both of these products are glutarimides, and both are hypnotics, yet their effects on the foetus are dramatically different.<sup>27</sup> The fact that congenital anomalies as well as exposures need to be considered at a granular rather than an aggregate level has considerable implications for the required sample size for evaluations of medicine safety in pregnancy.

The large number of pregnancies captured within the electronic healthcare databases described in this study and the fact that the data are routinely collected make them a valuable tool for evaluating medicine use during pregnancy. For medicines that are new to the market or used to treat less prevalent conditions, however, even these large databases may be less capable than pregnancy exposure registries of capturing an adequate sample of exposed pregnancies during a particular period.<sup>28,29</sup>

### *Exposure data*

The type of exposure data captured differed between databases, with the majority capturing prescription dispensing data whereas the UK databases captured all prescriptions issued. In France and Italy, only prescriptions reimbursed by the health service were captured.<sup>4,23,30</sup> One of the strengths of electronic healthcare databases is that prescription information is recorded prospectively and independently, by the prescriber or dispensing pharmacist, avoiding any maternal recall bias.<sup>31</sup> In addition, the level of detail available in terms of the specific product, the quantity and daily dose prescribed tends to be high, and these variables can often be used to calculate the duration and, hence, timing of potential exposure. Unlike exposure data obtained via a maternal interview, databases do not provide information on non-compliance and whether the patient took the medicine as directed. The likelihood of exposure misclassification may be less of a concern for databases capturing dispensed prescriptions than those capturing all prescriptions issued, but, in addition, knowledge of the extent and



type of prescriptions not captured in the database and the impact of these is important.

In database research, exposure misclassification can also occur as the result of inaccurate information on the LMP date. Only six of the eight databases contained this information, or the gestational age at delivery, for the majority of pregnancies. The potential for exposure misclassification resulting from inaccuracies in the LMP date will be greater for products prescribed for short-term use (e.g. antibiotics) than for those used long-term to treat chronic conditions.

### *Outcome data*

In all databases, with the exception of the IADB.nl database in the Netherlands, it was possible to identify congenital anomalies. Unlike pregnancy exposure registries and case–control surveillance systems, which often have the benefit of review by a consultant paediatrician or teratologist and very detailed information on the specific congenital anomaly, electronic healthcare databases often lack detail on anomalies, and researchers may have to rely on the entry of a single medical code. In general, databases that include links to medical birth registries and congenital anomaly registers such as EUROCAT are likely to contain the most detailed information on anomalies, and it is an objective of the EUROMediCAT project to pilot the linkage between healthcare databases and EUROCAT congenital anomaly registries, where they co-exist.

An advantage of some of the databases reviewed was their potential for capturing induced terminations in addition to pregnancies ending in a delivery. This is particularly beneficial given that many of the more serious congenital anomalies may be diagnosed prenatally and may subsequently be terminated. If such anomalies are caused by a medicine, but not captured, the analyses would fail to identify an increased risk. Some databases in this review allowed the identification of clinically recognised spontaneous as well as induced pregnancy loss, premature birth, low or high birth weight and intrauterine growth retardation.

### *Potential risk factors and confounders*

Surveillance systems that collect data from maternal interviews and questionnaires have the benefit of being able to request information on additional risk factors and potential confounders, whereas in databases, the availability of this information can be limited. In this review, UK primary-care databases contained the most information on the commonly considered potential confounding factors such as smoking status and alcohol consumption.

## CONCLUSION

Post-marketing surveillance systems are essential for evaluating the use and safety of medicines during pregnancy. This study suggests that, within Europe, electronic healthcare databases may be valuable sources of data that can provide information on medicine utilisation patterns, user characteristics and medicine safety during pregnancy. They may complement existing EUROCAT or case–control surveillance systems, especially where no pregnancy registry is in place. Given the potential of databases in the field of medication use in pregnancy, one aspect of the EUROMediCAT study will involve using the databases described in this paper to establish the extent and nature of use of antiepileptic drugs, antidiabetic medicines, asthma medicines and selective serotonin reuptake inhibitors during pregnancy in the different regions. It will explore the relationship between users of the four drug groups previously mentioned and other health behaviours and exposures in order to identify possible confounders and effect modifiers in drug teratogenicity studies. The findings of the medicine utilisation studies will then be used to inform other aspects of EUROMediCAT, which are focussing on linking selected electronic healthcare databases to EUROCAT congenital anomaly registries to study the safety of these medicines when used during pregnancy.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

### KEY POINTS

- Post-marketing surveillance systems are essential for evaluating the use and safety of medicines during pregnancy.
- Within Europe, electronic healthcare databases may provide valuable data on medicine utilisation patterns, user characteristics and medicine safety during pregnancy.
- Electronic healthcare databases in Europe have the potential to complement existing EUROCAT or case–control surveillance systems for evaluating medicine use and safety during pregnancy.

## ETHICS STATEMENT

Ethical and data access approvals were obtained from the relevant governance infrastructures where needed.

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## REFERENCES

1. Daw JR, Hanley GE, Greyson DL, *et al.* Prescription drug use during pregnancy in developed countries: a systematic review. *Pharmacoepidemiol Drug Saf* 2011; **20**(9): 895–902.
2. Andrade SE, Gurwitz JH, Davis RL, *et al.* Prescription drug use in pregnancy. *Am J Obstet Gynecol* 2004; **191**(2): 398–407.
3. Bakker MK, Jentink J, Vroom F, *et al.* Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; **113**(5): 559–568.
4. Gagne JJ, Maio V, Berghella V, *et al.* Prescription drug use during pregnancy: a population-based study in Regione Emilia-Romagna, Italy. *Eur J Clin Pharmacol* 2008; **64**(11): 1125–1132.
5. Lacroix I, Damase-Michel C, Lapeyre-Mestre M, *et al.* Prescription of drugs during pregnancy in France. *Lancet* 2000; **356**(9243): 1735–1736.
6. Bakker MK, Kolling P, van den Berg PB, *et al.* Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. *Br J Clin Pharmacol* 2008; **65**(4): 600–606.
7. Mitchell AA. Systematic identification of drugs that cause birth defects—a new opportunity. *N Engl J Med* 2003; **349**(26): 2556–2559.
8. Ehrenstein V, Sorensen HT, Bakker LS, *et al.* Medical databases in studies of drug teratogenicity: methodological issues. *Clin Epidemiol*. 2010; **2**: 37–43.
9. Greenlees R, Neville A, Addor MC, *et al.* Paper 6: EUROCAT member registries: organization and activities. *Birth Defects Res A Clin Mol Teratol* 2011; **91**(S1): S51–S100.
10. Dolk H, Jentink J, Loane M, *et al.* Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? *Neurology* 2008; **71**: 714–722.
11. Lyons R, Jones K, John G, *et al.* The SAIL databank: linking multiple health and social care datasets. *BMC Med Inform Decis Mak* 2009; **9**(1): 3. DOI: 10.1186/1472-6947-9-3
12. Wood L, Martinez C. The General Practice Research Database: role in pharmacovigilance. *Drug Saf* 2004; **27**(12): 871–881.
13. Ford D, Jones K, Verplancke J-P, *et al.* The SAIL databank: building a national architecture for e-health research and evaluation. *BMC Health Serv Res* 2009; **9**(1): 157. DOI: 10.1186/1472-6963-9-157
14. Coloma PM, Trifirò G, Schuemie MJ, *et al.* Electronic healthcare databases for active drug safety surveillance: is there enough leverage? *Pharmacoepidemiol Drug Saf* 2012; **21**(6): 611–621.
15. Coloma PM, Schuemie MJ, Trifirò G, *et al.* Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR project. *Pharmacoepidemiol Drug Saf* 2011; **20**(1): 1–11.
16. Lyng E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; **39**(7 suppl): 30–33.
17. Wallach Kildemoes H, Toft Sørensen H, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; **39**(7 suppl): 38–41.
18. Thygesen LC, Daasnes C, Thaulow I, *et al.* Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011; **39**(7 suppl): 12–16.
19. Schirm E, Tobi H, de Jong-van den Berg LTW. Identifying parents in pharmacy data: a tool for the continuous monitoring of drug exposure to unborn children. *J Clin Epidemiol* 2004; **57**(7): 737–741.
20. Espnes MG, Bjørge T, Engeland A. Comparison of recorded medication use in the Medical Birth Registry of Norway with prescribed medicines registered in the Norwegian Prescription Database. *Pharmacoepidemiol Drug Saf* 2011; **20**(3): 243–248.
21. Furu K, Wettermark B, Andersen M, *et al.* The Nordic countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol* 2010; **106**(2): 86–94.
22. Klungsoyr K, Morken NH, Irgens L, *et al.* Secular trends in the epidemiology of pre-eclampsia throughout 40 years in Norway: prevalence, risk factors and perinatal survival. *Paediatr Perinat Epidemiol* 2012; **26**(3): 190–198.
23. Lacroix I, Hurault C, Sarramon MF, *et al.* Prescription of drugs during pregnancy: a study using EFEMERIS, the new French database. *Eur J Clin Pharmacol* 2009; **65**(8): 839–846.
24. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the medical research council vitamin study. *Lancet* 1991; **338**(8760): 131–137.
25. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992; **327**(26): 1832–1835.
26. Boyd PA, Haeusler M, Barisic I, *et al.* Paper 1: The EUROCAT network—organization and processes. *Birth Defects Res Part A: Clin Mol Teratol* 2011; **91**(S1): S2–S15.
27. Heinonen OP, Slone D, Shapiro S. Sedatives, tranquilizers, and antidepressant drugs In: *Birth Defects and Drugs in Pregnancy*, Kaufman DWK (ed). Publishing Sciences, 1977; p. 343–344.
28. Charlton RA, Weil JG, Cunningham M, *et al.* Comparing the General Practice Research Database and the UK Epilepsy and Pregnancy Register as tools for postmarketing teratogen surveillance: anticonvulsants and the risk of major congenital malformations. *Drug Saf* 2011; **34**(2): 157–171.
29. Charlton RA, Cunningham MC, de Vries CS, *et al.* Data resources for investigating drug exposure during pregnancy and associated outcomes: the General Practice Research Database (GPRD) as an alternative to pregnancy registries. *Drug Saf* 2008; **31**(1): 39–51.
30. Hurault-Delarue C, Lacroix I, Vidal S, *et al.* Médicaments et grossesse: étude dans la base de données EFEMERIS 2004–2008. *Gynecol Obstet Fertil* 2011; **39**(10): 554–558.
31. Van den Brandt PA, Petri H, Dorant E, *et al.* Comparison of questionnaire information and pharmacy data on medicine use. *Pharm Weekbl Sci* 1991; **13**(2): 91–96.